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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/027,205	02/20/98	JUNE C	GIN-005

000959
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28 STATE STREET
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HM12/0207

EXAMINER	
ROARK, J	
ART UNIT	**PAPER NUMBER**
1644	16

DATE MAILED: 02/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/027,205	Applicant(s) JUNE ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 55-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 55-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jessica Roark, Art Unit 1644, Technology 1600.

2. The instant application is in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

3. The request filed on 7/21/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/027,205 is acceptable and a CPA has been established. An action on the CPA follows.

4. Applicant's amendment, filed on 7/21/2000 (Paper No. 13), is acknowledged.
Claims 2-54 have been canceled.
Claims 55-86 have been added.
Claims 1 and 55-86 *are pending.*

5. Applicant's election without traverse of the species of an anti-CD28 antibody in Paper No. 15 is acknowledged.

6. For examination of the CPA, it is noted that Applicant's amendment of claim 1 and cancellation of the previously pending claims has rendered the previous rejections moot, unless noted below.

7. The drawings filed on 2/20/98 are acceptable.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

Applicant is reminded "BALB/c" is the proper designation of this mouse strain (e.g. page 32, line 20).

9. For examination purposes claims 85 and 86 are interpreted to depend from claim 83.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 59, 64-74, 79, 81, 84 and 86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention.

With respect to methods of downregulating CXCR4 recited in claims 65-74, 79 and 84; Figure 4 and Example 7 disclose that the levels of mRNA for *CXCR4* are not downregulated after treatment of T cells with anti-CD28 antibody, rather CXCR4 mRNA levels *increase* after stimulation. Furthermore, the specification discloses that the infectivity of a CXCR4-dependent T-tropic virus is not blocked (e.g., Example 3 and figure 1). Therefore, the specification as-filed does not provide enabling support for the instant limitation of decreasing CXCR4 expression *in vitro*.

In addition, with respect to methods wherein the anti-CD28 is soluble (claims 59, 64, 69, 74, 81 and 86); the specification discloses on page 36 at lines 11-13 that *co-immobilization* of the anti-CD28 antibody with an anti-CD3 antibody is required for resistance to the M-tropic (i.e., CCR5-dependent) HIV isolate. Furthermore, the specification on page 35 at line 29 explicitly states that *soluble* anti-CD28 renders T cells sensitive to infection with M-tropic virus; indicating that CCR5 expression is not downregulated. Smithgall et al. (AIDS Res. and Human Retroviruses, 11:885-892 1995, IDS #DK) have also observed that *soluble* anti-CD28 increase cell sensitivity to HIV infection (e.g., "Abstract" and Figure 2). Similar observations have been made by Pinchuk et al. (Immunity 1:317-325 1994, IDS #DG; e.g. "Abstract" and Figure 3D). Therefore, the specification as-filed does not provide enabling support for the instant limitation of *soluble* anti-CD28 antibodies.

Given a disclosure that *soluble* anti-CD28 *increases* sensitivity to viral infection; the skilled artisan would not reasonably expect that expression of CCR5 would be downregulated by treatment with *soluble* anti-CD28. Likewise, given *in vitro* examples indicating an *increase* in expression of CXCR4 mRNA and the lack of objective evidence supporting a reasonable expectation that the outcome of the treatment would be different *in vivo*; the skilled artisan would not reasonably expect that CXCR4 expression would be downregulated either *in vitro* or *in vivo*. In both cases the lack of established protocols thus indicate a lack of predictability in the art to which the invention pertains. Therefore, absent a specific and detailed description in Applicant's specification of how to effectively practice the claimed methods, and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for downregulating CXCR4 expression; undue experimentation would be required to practice the claimed methods with a reasonable expectation of success.

12. Claims 1, 55-64, 75-78, 80-83 and 85-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of downregulating HIV-1 fusion cofactor expression comprising contacting the T cell with *co-immobilized anti-CD3 and anti-CD28*; does not reasonably provide enablement for either the full scope of *compounds comprising a CD28 ligand, or for anti-CD28 in the absence of anti-CD3*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses on page 6 at lines 4-7 that CD28 ligands include antibodies to CD28 as well as the natural ligands B7.1 (CD80) and B7.2 (CD86). Carroll et al. (Immunol. 10:195-202 1998) review the art recognized interaction of B7.1 and B7.2 with another molecule, CTLA-4 and discuss the observations that CTLA-4 ligation inhibits T cell signaling (see "the CD28/CTLA-4/B7 co-stimulation pathway" on pages 195-196). Carroll et al. also teach that CTLA-4 ligation *increases* CCR5 expression, even in the presence of CD28 stimulation (e.g. page 198, bridging paragraph of columns 1 and 2). Thus the CD28 ligands B7.1 and B7.2 would be expected to *increase* CCR5 expression because they bind both CD28 and CTLA4, but the CTLA4 effect is dominant (summarized at page 199, in "CD28/B7 co-stimulation pathways and HIV-1 infection *in vivo*", 2nd paragraph).

The specification discloses on page 36 at lines 11-13 that co-immobilization of the anti-CD28 antibody with an anti-CD3 antibody is required for resistance to the M-tropic (i.e., CCR5-dependent) HIV isolate. The specification on page 35 at line 29 also explicitly states that *soluble* anti-CD28 renders T cells sensitive to infection with M-tropic virus; indicating that CCR5 expression is not downregulated. Insufficient evidence is provided that immobilized anti-CD28 by itself downregulates CCR5 expression, since it appears that all experiments were carried out in the presence of immobilized anti-CD3.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The data disclosed in the specification as-filed and the teachings of Carroll et al. indicate that there are several non-functioning embodiments within the scope of the claims. Therefore, the experimentation left to those skilled in the art to identify other CD28 ligands that would function in the recited methods is unnecessarily, and improperly, extensive and undue. Likewise, the experimentation left to those skilled in the art to identify other formulations in which an anti-CD28 antibody would function in the claimed methods is unnecessarily, and improperly, extensive and undue.

Applicant should limit "comprising contacting the T cell with a CD28 ligand" to contacting the T cell with *co-immobilized anti-CD28 and anti-CD3*, as disclosed in the specification as-filed, to obviate this rejection.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Applicant's arguments in view of the evidence submitted as Appendices B and C of Paper #10 (filed 4/10/00) with respect to the previous rejection under 35 USC 112 are found convincing. The rejection with respect to the instant claims is withdrawn.

15. Claims 1 and 55-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1 and 55-86 are indefinite in their recitation of "downregulating (cofactor/CCR5/CXCR4) expression" because it is ambiguous as to whether mRNA or protein expression is downregulated. The specification on page 3 at lines 6-8 indicates techniques used for monitoring levels of mRNA (e.g., Northern blot) or protein (e.g., cell staining). However, expression of mRNA and protein has been shown to be discordant for CXCR4 Riley et al. (J. Virol. 72:8273-8280 1998; see page 8278, 2nd paragraph). Therefore, without an identification of whether "downregulating (cofactor/CCR5/CXCR4) expression" refers to mRNA or protein, the phrase is ambiguous, especially with respect to CXCR4.

B) Claims 85 and 86 recite the limitation "method of claim 3". There is insufficient antecedent basis for this limitation in the claim. It appears that the method of claim 83 is intended.

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

16. Given the rejections set forth supra under 35 U.S.C. 112, first paragraph, the following rejections with respect to prior art do not consider the non-enabled embodiments wherein the HIV-1 fusion co-factor is CXCR4, or wherein the CD28 ligand is other than co-immobilized anti-CD28 with anti-CD3.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.

18. Claims 1, 55-58, 82-83 and 85 are rejected under 35 U.S.C. 102(a) as being anticipated by Levine et al. (Science 272:1939-1942 1996, IDS #CH, see entire document).

Levine et al. teach a method for downregulating HIV fusion co-factor expression in a T cell by contacting the T cell with co-immobilized anti-CD3/anti-CD28 *in vitro* (see entire document). Levine et al. also teach that the T cells are activated (e.g., Figure 1A).

Although downregulation of the HIV-1 fusion co-factor CCR5 is not explicitly demonstrated, the use of identical methodology as that disclosed in the specification as-filed indicates that downregulation of CCR5 would be inherent; as indicated by the resistance of the T cells to infection with the M-tropic (CCR5-dependent) HIV-1strain.

When a claim recites using an old composition or structure (e.g. immobilized anti-CD3/anti-CD28 antibodies) and the use is directed to a result or property of that composition or structure (downregulation of CCR5), then the claim is anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant is reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency.

19. Claims 1, 55-58, 60-63, 75-78, 80, 82-83 and 85 are rejected under 35 U.S.C. 102(e) as being anticipated by Chang (US Pat. No. 6,129,916, see entire document).

Chang teaches and claims a method of activating T cells *in vivo* by contacting the T cells with co-immobilized anti-CD3/anti-CD28 (see entire document, especially claims 1-2 and columns 11-12). The use of such conjugates in vitro is also taught (e.g., column 5, especially lines 31-37).

Although downregulation of HIV-1 fusion co-factors including CCR5 is not explicitly demonstrated, the use of *in vivo* methodology equivalent to that disclosed in the specification as-filed for *in vitro* experiments indicates that downregulation of CCR5 would be an inherent outcome of these methods.

When a claim recites using an old composition or structure (e.g. immobilized anti-CD3/anti-CD28 antibodies) and the use is directed to a result or property of that composition or structure (downregulation of CCR5), then the claim is anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant is reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP 2112 - 2113 for case law on inherency.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
February 5, 2001

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